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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/779,560	HARBOE, MARIANNE	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 7/20/09 has been entered.

[2] Claims 44-77 are pending in the application.

[3] Applicant's amendment to the claims, filed on 7/20/09, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's remarks filed on 7/20/09 have been fully considered.

[5] In the interest of brevity, it is noted that the text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objection

[6] Claims 44 and 60 are objected to in the recitation of "a gene for encoding" and in order to improve claim form, it is suggested that the noted phrase be amended to recite, *e.g.,* "a gene encoding".

[7] Claim 48 is objected to as being dependent from claim 46 rather than claim 47 and Claim 51 is objected to as being dependent from claim 49 rather than claim 50.

[8] Applicant is advised that should claim 73 be found allowable, claim 77 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112, First Paragraph

[9] Claims 44-77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

The claims are drawn to a method using a medium that comprises chymosin activity and glucoamylase activity derived from the cultivation of an organism selected from a bacterial species, a yeast species, or a species of filamentous fungi, wherein the organism comprises a genus of genes "for encoding chymosin that is derived from a bovine or *Camelidae* species". Claims 57, 73, and 77 limit the *Camelidae* species to *Camelus dromedarius.* The claim requires that the encoded chymosin maintain at least 75% chymosin activity at a pH between 1.0 and 1.8.

According to the specification, the claimed method can be applied to "a medium that is derived from the cultivation of a recombinant microorganism that has an inserted gene expressing the aspartic protease" (paragraph bridging pp. 7-8), that the claimed method is applicable to "preparations of aspartic proteases derived from naturally produced aspartic protease by addition or deletion of one or more amino acids or substituting one or more amino acids herein" (specification at p. 8, lines 32-35) and states that the term "aspartic protease" includes pro-chymosin and chymosin (p. 8, line 24). The phrase "gene…derived from a bovine or *Camelidae* species" has been interpreted in light of the specification (p. 8, lines 32-35) as encompassing modified genes that are modified "by addition or deletion of one or more amino acids or substituting one or more amino acids". As such, the phrase "a gene for encoding chymosin that is derived from a bovine or *Camelidae* species" has been broadly, but reasonably interpreted in light of the specification as meaning a nucleic acid encoding naturally-occurring bovine and *Camelidae* species chymosin as well as mutant and variant forms thereof, wherein the mutant and variant forms are unlimited with respect to

structure. Also, it is noted that the genus *Camelidae* is not limited to any one species, but encompasses a plurality of species including, *e.g.,* alpaca, llama, vicunas, guanacos, bactrian camel and dromedarian camel.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the recited genus of genes that encodes a polypeptide with the recited functional characteristic of maintaining at least 75% chymosin activity at a pH of 1.0 to 1.8, i.e., a nucleic acid encoding wild-type bovine chymosin. Also, the instant remarks at p. 2 provide evidence that an mRNA encoding a wild-type *Camelus dromedarius* chymosin was known in the art at the time of the invention and further provides evidence that an *Aspergillus niger* transformed with an expression vector encoding wild-type *Camelus dromedarius* chymosin was known at the time of the invention. However, other than these disclosed

or known species, the specification fails to disclose other representative species of the genus of recited genes. In this case, the genus of recited genes encoding any chymosin polypeptide encompasses widely variant species, including, but not limited to genes encoding naturally occurring *Camelidae* chymosin from any species and any mutants and variants of bovine or *Camelidae* chymosin. The disclosure of the three representative species as noted above fails to reflect the variation among the members of the genus.

Therefore, given the lack of description of a representative number of compounds, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that appellant was in possession of the claimed invention.

RESPONSE TO ARGUMENT: Applicant argues an mRNA encoding a wild-type *Camelus dromedarius* chymosin was known in the art at the time of the invention as evidenced by EMBL accession number AJ131677 and further provides evidence that an *Aspergillus niger* transformed with an expression vector encoding wild-type *Camelus dromedarius* chymosin was known at the time of the invention as evidenced by US Patent 7,270,989. In view of these art-recognized species, applicant argues the genus of genes encoding chymosin and "derived from" a *Camelidae* species or "derived from" *Camelus dromedarius.* However, in view of a broad, but reasonable interpretation of the phrase "a gene for encoding chymosin that is derived from a bovine or *Camelidae* species" or a gene that is "derived from *Camelus dromedarius",* it is the examiner's

position that the specification and prior art fail to adequately describe the genus of recited genes at least for the reasons of record and those set forth above.

[10] Claim(s) 44-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method using a medium having bovine or *Camelus dromedarius* chymosin and *Aspergillus niger* glucoamylase activities and subjecting the medium to a pH of 1.0 to 1.8 to inactivate at least 50% of the glucoamylase activity, while maintaining at least 75% of chymosin activity, does not reasonably provide enablement for methods as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

"The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the

disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: The claims are drawn to a method using a medium that comprises chymosin activity and glucoamylase activity derived from the cultivation of a bacteria, a yeast, or a filamentous fungi comprising a gene encoding chymosin that is derived from a bovine or *Camelidae* species. Claim 39 limits the *Camelidae* species to *Camelus dromedarius.*

According to the specification, the claimed method can be applied to "a medium that is derived from the cultivation of a recombinant microorganism that has an inserted gene expressing the aspartic protease" (paragraph bridging pp. 7-8), that the claimed method is applicable to "preparations of aspartic proteases derived from naturally produced aspartic protease by addition or deletion of one or more amino acids or substituting one or more amino acids herein" (specification at p. 8, lines 32-35) and states that the term "aspartic protease" includes pro-chymosin and chymosin (p. 8, line 24). The term "derived" has been interpreted as encompassing a meaning of modified from an original source. As such, the phrase "a gene for encoding chymosin that is derived from a bovine or *Camelidae* species" has been broadly, but reasonably interpreted in light of the specification as meaning a nucleic acid encoding naturally-occurring bovine and *Camelidae* species chymosin as well as mutant and variant forms thereof, wherein the mutant and variant forms are unlimited with respect to structure. Also, it is noted that a *Camelidae* species encompasses alpaca, llama, vicunas, guanacos, bactrian camel and dromedarian camel.

The nature of the invention: As acknowledged by the instant specification, in the production of recombinant chymosin, additional undesired activities are also present in the culture medium, including situations where "the desired product is produced as a fusion protein…and a fusion partner...having...an undesired enzymatic side activity" (specification at p. 1), wherein the specification discloses the specific embodiment of bovine chymosin fused to *Aspergillus niger* var. *awamori* glucoamylase fusion protein as an example thereof (specification at p. 9, bottom). The invention involves reducing the pH of a culture medium comprising chymosin and glucoamylase to remove unwanted glucoamylase activity, while maintaining chymosin activity.

The state of the prior art; The level of one of ordinary skill; The level of predictability in the art: Methods for reducing unwanted side activities in a microbial culture medium by lowering pH were well-known at the time of the invention. See, *e.g.,* Lausten (US Patent 6,080,564, June 2000; cited in the PTO-892 filed on 4/9/02). Also, methods of recombinant production of bovine chymosin using a microbial expression host were well-known at the time of the invention. See, *e.g.,* Lawlis, Jr. et al. (US Patent 5,801,034, particularly column 2, lines 58-64; cited in the PTO-892 filed on 12/11/06) and Ward et al. (*Biotechnol* 8:435-440, abstract; cited in the IDS filed 16 April 2001).

Regarding the *Camelidae* species chymosin gene, in the instant remarks, applicant presents evidence that an mRNA encoding a wild-type *Camelus dromedarius* chymosin was known in the art at the time of the invention as evidenced by EMBL accession number AJ131677 and further provides evidence that an *Aspergillus niger*

transformed with an expression vector encoding wild-type *Camelus dromedarius* chymosin was known at the time of the invention as evidenced by US Patent 7,270,989.

Regarding the mutant and variant genes as encompassed by the claims, it is noted that the nucleotide sequence of an encoding nucleic acid determines the corresponding encoded protein's structural and functional properties, including its ability to maintain activity under a given set of conditions, *e.g.,* pH. Predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. As noted in prior Office actions, the state of the art provides evidence for the high level of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses an analysis of bovine chymosin and *Aspergillus niger* glucoamylase in an *Aspergillus niger* var. *awamori* culture medium at pH 1.6, 1.7,

1.8, and 5.6 after 21 hours. See Tables 2.1 and 2.2 at pp. 12-13 of the instant specification. The disclosed experimental evidence of Table 2.1 shows that bovine chymosin maintains approximately 87% of its activity at pH 1.6 to 1.8 relative to the activity at pH 5.6 after 21 hours, while Table 2.2 shows that *Aspergillus niger* glucoamylase loses substantial activity at pH 1.6 to 1.8 after 21 hours relative to its activity at pH 5.6. As noted above, the prior art discloses an mRNA encoding *Camelidae dromedarius* chymosin.

Also, the specification fails to provide guidance regarding the effects of pH treatment of any chymosin or glucoamylase, fails to provide guidance regarding alterations to bovine or *Camelidae dromedarius* chymosin that would enable it to maintain at least 75% activity at a pH of 1.0 to 1.8, and fails to provide guidance regarding the use of other glucoamylase polypeptides with an expectation that the activity of the glucoamylase will be inactivated by at least 50% or 90% at a pH of 1.0 to 1.8.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of making variants of a given polypeptide were known in the art at the time of the invention, e.g., mutagenesis, it was not routine in the art to screen for all genes as encompassed by the claims for those that encode a chymosin polypeptide having the desired activity under the recited conditions.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability, and the significant amount of non-routine experimentation required, undue experimentation

would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. As such, appellant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

RESPONSE TO ARGUMENT: Applicant argues an mRNA encoding a wild-type *Camelus dromedarius* chymosin was known in the art at the time of the invention as evidenced by EMBL accession number AJ131677 and further provides evidence that an *Aspergillus niger* transformed with an expression vector encoding wild-type *Camelus dromedarius* chymosin was known at the time of the invention as evidenced by US Patent 7,270,989. In view of these art-recognized working examples, applicant argues the genus of genes encoding chymosin and "derived from" a *Camelidae* species or "derived from" *Camelus dromedarius.* However, in view of a broad, but reasonable interpretation of the phrase "a gene for encoding chymosin that is derived from a bovine or *Camelidae* species" or a gene that is "derived from *Camelus dromedarius",* it is the examiner's position that the specification and prior art fail to enable the full scope of the recited genes at least for the reasons of record and those set forth above.

Claim Rejections - 35 USC § 103

[11] Claims 60-62, 66-71, and 73-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Lawlis, Jr. et al. (US Patent 5,801,034; hereafter "Lawlis"; cited in the PTO-892 filed on 12/11/06) and Ward et al. (*Biotechnol* 8:435-440; cited in the IDS filed 16 April 2001; hereafter "Ward").

The claims are drawn to a method for reducing glucoamylase activity in a milk clotting composition comprising the steps of: (i) providing a medium having a pH of 2.0 or higher that comprises chymosin activity and glucoamylase activity and is derived from the cultivation of an organism selected from a bacterial species, a yeast species, and a species of filamentous fungi, wherein the organism comprises a gene encoding a chymosin derived from a bovine or *Camelidae* species; and (ii) lowering the pH of said medium to a pH in the range of 1.0 to 1.8 by addition of an inorganic acid, and (iii) subjecting said medium to a pH in the range of 1.0 to 1.8 for a time sufficient to inactivate at least 50% of said glucoamylase activity while maintaining at least 75% of chymosin activity.

The reference of Lawlis teaches, "[i]n the various processes of culturing or fermenting microorganisms, it is sometimes necessary during or at the conclusion of the fermentation process to be able to kill the active cells in the mixture so that the desired product can be recovered from the culture or fermentation mixture. This is particularly true when microorganisms containing recombinant DNA are grown as production hosts and it is desirable to prevent any viable recombinant organisms from being released into

the environment" (column 1, lines 18-25). Lawlis teaches, "[i]n the development of this invention, it has been found that the change in pH alone of a fermentation mixture does not accomplish a complete or substantially complete cell kill. For example, in a culture of *Aspergillus niger* for the production of chymosin, reducing the pH to about 2 using sulfuric acid does not accomplish a complete or substantially complete cell kill" (emphasis added; column 2, lines 58-64). To achieve a substantially complete cell kill, Lawlis teaches "selecting a compatible organic acid…adjusting the pH of the culture to a value equal to or less than about 2 pH units below the pK_a of a selected compatible organic acid and adding a sufficient amount of the selected compatible organic acid and/or salt (column 2, lines 29-39). Lawlis expressly teaches acetic acid, propionic acid, and formic acid as being used in the claimed method (see claim 2) and further teaches "if formic acid (pK_a =3.75) is to be used to accomplish the cell kill, the pH of the mixture will be adjusted with a mineral acid to about 1.75 or less, then formic acid is added to accomplish the cell kill" (column 3, lines 51-60). See also claims 2 and 3 of Lawlis, which specifically recites the use of formic acid as the organic acid and sulfuric acid as the mineral acid in the disclosed method. The working examples of Lawlis, although using acetic acid and not formic acid, teach that "substantially complete cell kill" can be achieved by overnight incubation (Example 1), a 60 hour incubation (Example 2), and a 4 hour incubation (Example III). Although Lawlis teaches the method be applied to a culture of *Aspergillus niger* for the production of chymosin (column 2, lines 58-64) and also specifically teaches adjusting the pH the of the mixture with a mineral acid, which

as noted above is expressly taught as sulfuric acid in claim 3, to about 1.75 or less when formic acid is the selected organic acid (column 3, lines 51-60).

While Lawlis teaches and/or suggests applying the method to a culture of *A. niger* for the production of chymosin, Lawlis does not expressly teach or suggest applying the method to a medium comprising bovine or *Camelidae* chymosin and glucoamylase activities.

The reference of Ward teaches *Aspergillus niger* var. *awamori* comprises a gene encoding a glucoamylase polypeptide (p. 435, column 1, bottom; column 2, middle; and p. 437, column 2, top) and further teaches the use of an expression vector in which the cDNA encoding a bovine prochymosin B polypeptide was fused in frame immediately following the codon for the last amino acid of *Aspergillus niger* var. *awamori* glucoamylase gene and recombinant production of chymosin in *A. niger* var. *awamori* transformed with this vector "led to the secretion of considerably higher amounts of chymosin than obtained with previous chymosin vectors" (p. 435, left column, abstract). See also p. 437, right column, Table 2. According to Ward, the *A. niger* var. *awamori* medium comprising the secreted fusion exhibited chymosin activity and glucoamylase activity (p. 437, right column, Table 2).

Therefore, at the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Lawlis and Ward to use a culture of the transformant of Ward in a method of Lawlis, namely, treating the culture with sulfuric acid to a pH of 1.75 and then adding formic acid to effect substantial cell kill. One would have been motivated to use the transformant of Ward in the method of Lawlis because

the transformant of Ward produces "considerably higher amounts of chymosin." One would have had a reasonable expectation of success for using the culture of Ward in the method of Lawlis because of the teachings of Lawlis and Ward. Therefore, the method of claims 60-62, 66-71, and 73-77 would have been obvious to one of ordinary skill in the art at the time of the invention.

The following comments are provided to clarify the instant rejection. Regarding the limitation, "subjecting said medium...for a period of time sufficient to inactivate at least 50% of said glucoamylase activity while maintaining at least 75% of said chymosin activity" in claim 9, according to MPEP 2111.01.I, "'[c]laims are not to be read in a vacuum, and limitations therein are to be interpreted in light of the specification in giving them their broadest reasonable interpretation'". Thus, although claim 60 does not specifically delineate the recited "period of time", the examiner has referred to the specification and claims to ascertain that which is intended as being encompassed by the "period of time". According to the specification at p. 7, lines 21-23, "[t]ypically…the required treatment period is within the range of 0.1 minutes to 48 hours", which is as few as 6 seconds up to 48 hours. See also the limitations of claim 71, which limit the "period of time" in claim 60 to between 0.1 minutes to 48 hours. Accordingly, the examiner has interpreted the "period of time" to inactivate at least 50% or 90% of the glucoamylase activity, while maintaining at least 75% or 85% of the chymosin activity as being inclusive of 0.6 seconds up to 48 hours.

According to MPEP 2112, "[t]he express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or

103. 'The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness'". MPEP 2112.I states, "'[t]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer". MPEP 2112.IV states, "'To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill". While it is acknowledged that the combination of references fails to *expressly* teach inactivation of at least 50% or 90% of the glucoamylase activity, while maintaining at least 75% or 85% of the chymosin activity, this would be a necessary feature of practicing the method of Lawlis with a culture medium of the transformant of Ward producing a glucoamylase-chymosin fusion protein, particularly as Lawlis expressly teaches treating a culture medium at a pH of 1.75 with overnight incubation or incubation for 4 hours, which pH and time are either specifically recited and/or disclosed in the specification to achieve the desired reduction in glucoamylase activity while maintaining the desired level of chymosin activity. Thus, although the prior art does not *expressly* teach the noted limitation, since the pH and time of the prior art method are encompassed by the "period of time", practicing the prior art method would appear to necessarily result in the inactivation of at least 50% or 90% of the glucoamylase activity, while maintaining at least 75% or 85% of the chymosin activity as required by the claims.

Regarding the limitation "the gene encoding chymosin is derived from *Camelus dromedarius*" in claims 73 and 77, as noted above, the specification describes such "derived" genes as encompassing a gene encoding chymosin having any structure, the gene of Ward has been reasonably interpreted in light of the specification as being encompassed by the claims.

[12] Claims 44-46, 50-51, 55, and 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Lawlis and Ward as applied to claims 60-62, 66-71, and 73-77 above and further in view of Chang ("Chemistry", McGraw Hill Inc., New York, 1991, p. 734), and Van Ooijen (US Patent 5,371,287; hereafter "Van Ooijen").

The teachings of Lawlis and Ward are set forth above. Lawlis further teaches "The 'organic acid' employed to effect a substantially complete kill can be any suitable and compatible acid having 1 to about 5 carbon atoms" (column 3, lines 30-32). Lawlis does not teach using lactic acid in the disclosed method.

The reference of Chang teaches lactic acid is a 3-carbon organic acid (p. 734, bottom).

The reference of Van Ooijen teaches the pKa of lactic acid is 3.08 (p. 4211, column 1).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Lawlis, Ward, Chang, and Van Ooijen to use a culture of the transformant of Ward in a method of Lawlis, using lactic acid at a pH of 1.08. One would have been motivated to use lactic acid in the method of Lawlis

because lactic acid satisfies the criteria of Lawlis, *i.e.,* it is an organic acid and has 3 carbons. One would have been motivated to use a pH of 1.08 because Lawlis expressly teaches using a pH of a value equal to or lower than 2 pH units below the pKa of the organic acid (column 2, lines 32-34). One would have had a reasonable expectation of success to use lactic acid at a pH of 1.08 in the method of Lawlis because of the teachings of Lawlis, Chang, and Van Ooijen. Therefore, the method of claims 44-46, 50-51, 55, and 57-59 would have been obvious to one of ordinary skill in the art at the time of the invention.

[13] Claims 44-46, 50-55, and 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Lawlis and Ward.

The teachings of Lawlis and Ward are set forth above. Lawlis further teaches that acetic acid is preferred due to its low cost and effectiveness (column 4, lines 49-53). Lawlis teaches that when acetic acid is used, the pH is adjusted to "about 2.75 *or below* by the addition of...sulfuric acid, then the acetic acid is added" (emphasis added). Lawlis teaches using acetic acid at a pH of 2.0 as an example of a pH *below* 2.75 (column 6, Example II). Lawlis does not teach using acetic acid at a pH of 1.75.

However, at the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Lawlis and Ward to use a culture of the transformant of Ward and treating the culture with acetic acid at a pH of 1.75 to effect substantial cell kill. One would have been motivated to use the transformant of Ward in the method of Lawlis because the transformant of Ward produces “considerably

higher amounts of chymosin." One would have been motivated to use acetic acid because it is a "preferred" organic acid. One would have been motivated to use a pH of 1.75 because Lawlis expressly teaches using acetic acid at a pH of 2.75 *or less,* and while a pH of 1.75 is specifically exemplified with respect to formic acid, one of ordinary skill in the art would have recognized this pH as being a pH below 2.75 and thus applicable for use with acetic acid. One would have had a reasonable expectation of success to use a culture of the transformant of Ward and treating the culture with acetic acid at a pH of 1.75 to effect substantial cell kill because of the teachings of Lawlis and Ward. Therefore, the method of claims 44-46, 50-55, and 57-59 would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO ARGUMENT: Applicant argues in view of the recited limitation to require the use of an inorganic acid (claim 60) or the use of "lactic acid, acetic acid, propionic acid, or citric acid" (claim 44), there would be no reason to lower the pH to meet the claimed range when practicing the method of Lawlis.

Applicant's argument is not found persuasive. Regarding the use of an inorganic acid, Lawlis expressly teaches lowering the pH to the recited range using sulfuric acid, which is interpreted as being an "inorganic acid". Regarding the use of lactic acid, acetic acid, propionic acid, or citric acid, while Lawlis does not expressly teach using lactic acid, the combination of references as noted above teaches or suggests using lactic acid in the method of Lawlis. At least for the reasons set forth above, the claimed

invention would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

[14] Status of the claims:

- Claims 44-77 are pending.
- Claims 44-77 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656